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ONTARIO HEALTH TECHNOLOGY ADVISORY COMMITTEE

PET SCAN PRIMER

A Guide to the Implementation of Positron Emission Tomography Imaging in Ontario

Prepared by the Members of the Ontario PET Steering Committee

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Ontario

Ministry of Health and Long-Term Care

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In Brief

What is PET?

Positron Emission Tomography (PET) is a nuclear medicine diagnostic imaging exam. Nuclear medicine exams use small amounts of radioactive material (known as radiopharmaceuticals) that are usually injected into a person's bloodstream but are sometimes swallowed by mouth or inhaled as a gas. The most common radiopharmaceutical used in PET scanning is ^{18}FDG (Fluorodeoxyglucose). Health Canada regulates ^{18}FDG as a new product and authorizes only licensed manufacturers to distribute it to PET scanning centres. The use of ^{18}FDG is subject to a Clinical Trials Agreement unless the institution applies for a Notice of Compliance to manufacture the radiopharmaceutical for a specific indication and maintains an Establishment License. ^{18}FDG is a form of sugar and is taken up avidly by many cancers because cancers use sugar for growth. However, metabolically active normal tissues like the brain, as well as benign conditions such as inflammation, also take up ^{18}FDG. Imaging exams, such as plain radiography, ultrasound, computed axial tomography (CAT or CT) and magnetic resonance imaging (MRI) are routinely used to provide information on the shape and size of anatomical structures and this information is used for both diagnosis and treatment decision-making. However, PET scanning can provide information on both the location and the extent of metabolic activity of abnormal tissues such as cancer and it has the potential to identify areas of abnormal metabolic activity before there is distortion of the anatomy. The key question is does the information from PET make a difference in the clinical management of patients compared to these other tests?

How do PET Scanners Work?

A PET scanner works with a computer to create two- and three-dimensional images of the structure and function of organs and tissues. This technology is useful in determining the stage (extent) of some cancers, which in turn may help to define the most appropriate treatment for the stage of cancer.

Like any diagnostic test, PET must be used based on evidence because it can pose risks, as well as benefits. PET scanning can give false results if chemical balances within the body are not normal. As well, cancers that do not take up ^{18}FDG may give a negative PET scan. If the PET scan upstages cancer accurately (i.e., the cancer is more serious than it was originally thought to be) patients can avoid aggressive treatments that will not help them. However, if the PET scan upstages the cancer incorrectly, patients with potentially curable cancers risk not getting the most appropriate treatment for their cancer or they may get aggressive treatments they do not need. Of particular concern is the recent report from the U.S. that 70% of patients who were scheduled to have a biopsy (the gold standard for diagnosing cancer is biopsy followed by pathological exam) before a PET scan ended up not having a biopsy and having treatment based on their PET scan results alone. The PET scan was three times more likely to lead to treatment than non-treatment, with physicians changing the management of 36.5% of their patients after the PET scan.

How Do Patients Access PET Scans in Ontario?

A provincial PET Steering Committee makes recommendations on the appropriate use of PET to the Ministry of Health and Long-Term Care's Ontario Health Technology Advisory Committee. The Committee is made up of representatives of the Institute for Clinical Evaluative Sciences, Cancer Care Ontario, and the

Program for Assessment of Technology in Health, clinical oncologists, nuclear medicine physicians and experts in clinical research trials.

PET is available in three ways in Ontario.

1. PET is funded for those cancers where there is enough evidence that the test improves the clinical management of specific cancers or other conditions. To enable Ontarians to have a PET scan where evidence supports its use and to comply with Health Canada's regulations for the use of ^{18}FDG, the ministry established cancer and cardiac PET registries. Patients receiving PET scans for their cancer or cardiac conditions must be recorded in a "registry" with information on the reason for and the results of the PET scan. Over 1,400 patients are enrolled in the PET registries to date.

2. High quality clinical trials are being conducted to determine if PET improves diagnosis and treatment decisions for early stage lung cancer, stage III (locally advanced) lung cancer, women with breast cancer, head and neck cancer, and colorectal cancer that has spread to the liver. The result of the trial in early stage lung cancer was presented at the American Society of Clinical Oncology meeting in June 2008. It showed that PET is more effective than standard staging studies in determining which patients have the greatest probability of benefit from surgery. As a result, PET is now funded for all Ontario patients with early non-small cell lung cancer who are being considered for surgery. This is projected to increase the number of PET scans in Ontario by over 1,000 in the next 12 months. The breast cancer trial has also been completed and is being analysed, and the other three trials are well on their way to completion. Over 1,500 patients are enrolled in the clinical trials.

3. Situations where a PET scan may be justified but cannot be obtained through the clinical studies or registries are adjudicated by an expert panel. Physicians who think that their patient might benefit from a PET scan can refer them to the PET Access Program where requests are reviewed by a panel of oncologists, radiologists and nuclear medicine physicians. Between October 2006 and March 31, 2008, 170 applications were made to the Ontario PET Access Program; 68 applications for a PET scan were approved.

What Does The Research Say About PET Scans?

A review by the Institute for Clinical Evaluative Sciences in 2001 found little evidence to show that PET made a significant difference in most of the clinical conditions that were reviewed. The International Network of Agencies for Health Technology Assessment – after conducting a survey of 19 countries in 2004 – concluded that all countries need to undertake continuous quality improvement to manage the uncertainty about the evidence for PET.

Clinical experts believe there is clear evidence that PET improves the diagnosis and treatment of patients with the following conditions:

- Solitary pulmonary nodules in cancer patients who cannot have a biopsy, who have failed prior biopsy attempts or in whom the potential risk of a biopsy-induced pneumothorax is high.
- Patients with treated thyroid cancer, treated germ cell cancer or treated colorectal cancer who develop positive biomarkers (an elevated biological marker usually indicates that disease is present) but whose CT/MRI does not show that the cancer has recurred.

- Patients being considered for surgical resection of a non-small cell lung cancer.
- Certain specific indications for lymphoma.
- Assessment of the probability of the recovery of heart muscle function after coronary revascularization (Myocardial viability studies).

Ontario has been leading the way in studying the clinical benefits of PET and other jurisdictions are undertaking similar evaluations. For example, the U.S. Centers for Medicare and Medicaid introduced a "Coverage with Evidence Development" policy which requires physicians to provide information on the usefulness of PET to clinically manage cancer conditions that were not previously covered.

Do All the Other Provinces Provide Access to PET Scans?

Ontario has 10 hospital-based PET scanners, more than any other province. However, the other larger provinces (Quebec, British Columbia and Alberta) perform more scans. Ontario clinical experts believe that some of these PET scans are conducted for indications that do not have sufficient evidence of clinical benefit.

What Are the Costs Associated with PET?

The current average cost to perform a PET scan in Ontario is $1,000-$1,200 per scan which includes the cost of the radiopharmaceutical and a stipend (payment) for the physician reading the scan.

PET in the Future

Some believe that PET should be widely available based on the claim that this technology improves care and saves lives. Others believe that PET should be used in situations where it has been shown in well conducted studies to add value and provide additional accurate information to improve the diagnosis and subsequent treatment of patients.

Clinical trials research is the best approach to obtain evidence for PET scanning. Ontario's trials are leading to greater understanding of how PET can benefit patients. However, there has been some concern about the pace of the clinical trials in Ontario. Clinical trials take time and involve many steps including the development of a research protocol and quality assurance standards, getting Research Ethics Board approvals and enrolling a sufficient number of patients, which relies on the willingness of physicians to approach their patients and the acceptance of patients to participate in the trial.

Although Ontario's clinical trials are taking time, they are resulting in high quality – and internationally recognised – evidence for the appropriate use of PET in diagnosis and treatment. This evidence is critically important for the safety and care of Ontarians.

To improve access to PET for clinically-proven conditions, Ontario is urging Health Canada to simplify its regulations for accessing ^{18}FDG. Health Canada regulates ^{18}FDG as a new product and requires a Clinical Trials Agreement for all non-approved indications. Currently, in Ontario, only Hamilton Health Sciences manufactures an approved ^{18}FDG product for lung cancer indications, including diagnosis of solitary pulmonary nodules, staging of non-small cell lung cancer and evaluation of recurrence of non-small cell lung

cancer. This meaans that Ontario and other provinces have had to set up PET registries to provide access for other indicatioons in cancer and cardiac disease of established clinical utility. At present, the process to follow in order to access PET through the registries is not widely known by physicians. Regular communications through OHIP Bulletins and other means should increase physicians' awareness of how to access PET for their patients.

Ontario remains committed to an evidence-based approach to the introduction of new technologies including PET. Given the competing demands for limited health care resources, the risks associated with diagnostic imaging procedures (all procedures have risks including the risk of false positives and false negative results), and the potential for the technology to affect patient outcomes significantly, PET's usefulness needs to be established before it becomes part of routine clinical practice. Ontario is making a valuable contribution to the appropriate and effective use of this new technology in Ontario and internationally.

1 Introduction and Overview

This document presents information on Positron Emission Tomography or PET scanning. The document begins by defining PET scanning and explaining how it works (Section 2). Section 3 describes how PET scanning is used followed by a discussion of whether PET scanning makes a difference to patient care (Section 4).

Section 5 describes Ontario's evidence-based approach to PET scanning which includes:

- Access to PET through high quality clinical trials (5.1);
- Access to PET through registry studies (5.2);
- Access to PET through the PET Access Program (5.3);
- Quality assurance standards for PET (5.4);
- Ontario's PET infrastructure (5.5);
- Coordination of the PET program (5.6); and
- Communications (5.7).

Section 6 gives an overview of the definitive evidence for PET scanning, followed by the experience with PET scanning in other jurisdictions (Section 7). Final observations on the critical role of evidence to support PET scanning for quality patient care are then provided in Section 8.

2 What is Positron Emission Tomography (PET) Scanning and How Does it Work?

Positron Emission Tomography (PET)

is a diagnostic imaging exam. Diagnostic imaging is essential for diagnosing injury and a wide range of diseases. Imaging can also help determine the extent of disease and the most appropriate treatment for conditions such as cancer and heart disease. Imaging exams include radiography, ultrasound, computed axial tomography (CAT or CT), magnetic resonance imaging (MRI) and nuclear medicine (which includes PET). An overview of the types of diagnostic imaging exams, including PET, is presented below.[1]

Radiography

Radiography is the conventional imaging technique that uses ionizing radiation (X-rays). An image is made by passing X-rays through the body from an outside source.

Ultrasound

Ultrasound uses ultrasound waves rather than ionizing radiation to create images of organs and arteries.

Computed Axial Tomography (CAT or CT)

CTs use conventional X-rays to generate three-dimensional or axial images (around an axis) of all parts of the body. A CT scan combines a sophisticated X-ray system and a high-speed computer to produce slices

1 Cancer Care Ontario. 2004 (June). "Diagnostic Imaging" GTA 2014 Cancer Report.

of information. The CT produces cross-sectional pictures of the body that include details of the tissue and bone structure.

Magnetic Resonance Imaging (MRI)

MRIs use a magnetic field that is altered with radiofrequency waves to examine body tissue. Using a large magnet, radio waves and a computer, an MRI scans the patient's body and produces two- and three-dimensional images of the structure of body tissues and organs. For certain areas in the body such as the brain and spinal cord, MRI provides better images than CT.

Nuclear Medicine

Nuclear medicine exams use small amounts of radioactive materials that are injected into a person's bloodstream, swallowed by mouth or inhaled as a gas.[2] This radioactive material – known as a radiopharmaceutical or radiotracer – collects in the area of the body being examined. The material gives off energy in the form of gamma rays that come from areas of the body where the radioactive material has concentrated. This information can be used to diagnose or treat disease and other abnormalities.

Positron Emission Tomography

(PET) is a nuclear medicine technology. The PET scanner is a large machine with a round, doughnut shaped hole in the middle, similar to a CT unit. The scanner has multiple rings of detectors that measure the absorption of the radiopharmaceutical in a person's body. The scanner produces an image based on the energy given off by the different amounts of radiopharmaceutical absorbed by different cells in the body. For example, cancer cells may absorb more radiopharmaceutical than normal tissue, whereas cardiac scar tissues absorb less radiopharmaceutical than surrounding normal heart tissue. The PET scanner works with a computer to create two- and three-dimensional images of the structure and function of organs and tissues. The PET scan can help determine how well organs and tissues are functioning by measuring such things as blood flow, oxygen use and sugar (glucose) metabolism. The average amount of time required for each scan varies from 30 minutes for a brain scan to 60 minutes for a whole body scan. A PET scan can be combined with a CT scan (i.e., PET/CT scan) to better delineate the anatomical location of the energy given off by the radiopharmaceutical.

PET scanning depends on access to radiopharmaceuticals. The most common radiopharmaceutical used in PET scanning is ^{18}FDG (Fluorodeoxyglucose). Health Canada has strict regulations for the use of positron emitting radiopharmaceuticals including ^{18}FDG. Health Canada regulates ^{18}FDG as a new product and authorizes specific manufacturers to distribute it to PET scanning centres. The use of ^{18}FDG is subject to a Clinical Trials Agreement[3] for all non-approved indications unless the institution applies for a Notice of Compliance to use the radiopharmaceutical for a specific indication and maintains an Establishment License.[4] In Ontario, only McMaster University Medical Centre (Hamilton Health Sciences Corporation) has been awarded a Notice of Compliance for ^{18}FDG and then, only for lung cancer indications.

2 RadiologyInfo: A website of the Radiological Society of North America. http://www.radiologyinfo.org/en/info.cfm?pg=PETAbout-1. Accessed May 18, 2008.

3 Clinical trials are research aimed at improving the current standard of care. In many cases, experimental drugs and therapies are only approved for research purposes and so voluntary enrolment in a clinical trial is the only way for patients to access these treatments.

4 Unpublished draft briefing note: Issues Regarding the Supply of Positron Emitting Radiopharmaceuticals (PERs) by the Ontario PET Clinical and Research Imaging Centres (November 2007). Provided by Dr. Karen Gulenchyn, June 6, 2008.

PET scanning depends on timely access to positron-emitting isotopes. These isotopes are combined with organic compounds such as sugar to develop radioisotopes which are used in PET scanning. Positron-emitting isotopes are generated in a particle accelerator or cyclotron, and must be used soon after they are created since they decay quickly and become less effective. A cyclotron facility has to be located within a few hours travel time from where the PET scan is being performed.

Although PET scanning provides more detailed functional information than other diagnostic tools, PET scanning has a number of limitations and risks:

- The resolution of structures of the body with PET may not be as clear as with other imaging techniques, such as CT or MRI. As noted above, using both a PET scan and a CT scan can better identify where abnormalities are located in the body. PET/CT is replacing PET scanning alone in most jurisdictions around the world.
- Although PET has not been shown to have any side-effects in patients, PET scanning uses ionizing radiation which can be a health hazard in high doses, and must be kept to a minimum.[2] The long-term health risks associated with all types of imaging are not known. Radiologists support the ALARA principle – radiation dose As Low As Reasonably Achievable – to limit exposure to harmful radiation.[3]
- There is potential harm to individuals working with radiopharmaceuticals including people who produce, transport, prepare and administer the substance used in scanning.
- PET scanning can give false results if chemical balances within the body are not normal. For example, test results in diabetic patients or patients who have eaten within a few hours prior to the examination can be adversely affected because of altered blood sugar or blood insulin levels.
- Other disease processes such as infection or inflammation take up ^{18}FDG and may give the false impression of cancer when cancer is not present.
- PET scanning may identify abnormalities in cancer patients beyond those detected by CT and MRI. This "upstaging" of cancer – where the cancer appears to be more extensive than originally thought – can be helpful in making a treatment decision. If the PET scan upstages the cancer accurately, patients can avoid aggressive treatments that will not help them. However, if the PET scan upstages the cancer incorrectly, patients with potentially curable cancers run the risk of not getting the most appropriate treatments or they may get aggressive treatments that they do not need for their condition.
- A normal PET scan can help to rule out cancer and avoid biopsy in some cases where cancer is suspected. However, if the PET scan is falsely normal (not all cancers take up ^{18}FDG) then this will lead to a delay in diagnosis and potentially, a worse outcome.

  Cancers that have been treated with chemotherapy or radiotherapy may have fewer cancer cells to absorb the radiopharmaceutical and produce a negative scan.

3 How is PET Scanning Used?

PET was developed in the mid 1970s. PET was first used clinically for brain imaging but over the past 15 years, there has been increasing interest in and use of PET to diagnose cancer, heart disease and neurological conditions. During this time: i) PET technology has improved; ii) there has been more research on the use of PET to diagnose and treat various clinical conditions; iii) the United States Federal Drug Administration changed its regulations on the use of radioisotopes; iv) the American Medicare program and third party payers (such as insurance companies) increased funding for PET scanning which resulted in a large increase in the number of scans; and v) some medical groups have effectively lobbied to increase the use of PET in various provinces and countries.[9]

4 Does PET Scanning Make a Difference?

Certain diagnostic imaging exams are gradually replacing other imaging tests. For example, MRI and CT are gradually replacing – either partially or totally – other imaging procedures such as plain radiographs (i.e., X-rays), many nuclear medicine procedures, diagnostic cerebral angiography, and peripheral angiography.[10] Will PET replace other diagnostic imaging exams?

There is no doubt that PET scanning produces different information than other imaging techniques. For example, CT and MRI provide images of the structure of tissue and organs based on anatomy whereas PET provides images of the structure and function of tissue and organs that reflect biochemical processes and blood flow. The key question is, does this additional information make a difference in the diagnosis and treatment of patients compared to other tests such as MRI and CT?

PET scanning can potentially be used to detect cancer, determine how much a cancer has spread in the body, assess the effectiveness of a treatment plan and determine if cancer has returned after treatment. Other imaging techniques such as CT and MRI are already being used to answer these questions. Does performing a PET scan provide additional accurate information that would improve the diagnosis or subsequent treatment of all or certain cancers?

Similarly, PET scanning can help determine blood flow to the heart muscle, determine the effects of a heart attack (myocardial infarction) on areas of the heart, and identify areas of the heart muscle that would benefit from a procedure such as angioplasty[11] or coronary artery bypass surgery. Other imaging procedures such as diagnostic coronary angiography, MRIs and CTs are already being used to answer these questions. Does performing a PET scan provide additional accurate information that would improve the diagnosis or treatment of certain heart conditions?

9 Institute for Clinical Evaluative Sciences. 2001 (May) Health Technology Assessment of Positron Emission Tomography (PET) – A Systematic Review. An ICES Investigative Report.

10 MRI and CT Expert Panel (Dr. Anne Keller, Chair). 2005 (April). MRI and CT Expert Panel Phase One Report. Prepared for the Ontario Wait Time Strategy.

11 A procedure that widens coronary arteries that have been narrowed by atherosclerosis.

PET scanning can also be used to evaluate brain abnormalities such as tumours, memory disorders and seizures and other central nervous system disorders. Other imaging techniques such as diagnostic cerebral angiography, MRI and CT are already being used in these areas. Does performing a PET scan provide additional accurate information that would improve the diagnosis or treatment of certain neurological conditions?

These are important questions. It is tempting to assume that the use of newer, more sophisticated technology will automatically lead to better care and better health outcomes, but there is no rational reason for this to be automatically true. The benefits over and above the existing technology need to be demonstrated. The goal in each clinical situation must be to identify the diagnostic imaging technique that results in an accurate diagnosis and the most appropriate treatment for the patient provided in the safest and most effective and efficient manner.

5 Ontario's Evidence-Based Approach to PET Scanning

In 1999, the Ontario Association of Nuclear Medicine urged Ontario's Ministry of Health and Long-Term Care (the ministry) to fund the use of PET scanning for oncology (cancer), cardiology (heart) and neurology. The association argued that the usefulness of PET in these three situations was well established.

In response to this request, a provincial committee made up of the ministry, the Ontario Medical Association and the Ontario Hospital Association commissioned the Institute for Clinical Evaluative Sciences (ICES) to review the literature and summarize the evidence about the diagnostic accuracy of PET and its impact on patient outcomes. ICES reviewed the literature in:

- Oncology: lung cancer, solitary pulmonary nodules, head and neck cancer, breast cancer, malignant lymphoma including Hodgkin's disease, melanoma, colon cancer, differentiating scar tissue due to cancer treatment from the recurrence of cancer in patients with brain tumours.
- Cardiac disease: cardiac viability and coronary artery disease.
- Neurological disease: intractable epilepsy and dementia.

In its review of the literature up to December 2000, ICES commented that "despite the availability of PET scanning for almost three decades, the number of methodologically high quality studies (and the numbers of patients within these studies) is distressingly small."[12] The review concluded that PET scanning should only be used if the results of the test would affect patient management. The review found that there was insufficient evidence to show that PET made a significant difference in most of the clinical conditions the review covered. The ICES report made recommendations in three major areas:

- Oncology (cancer): The ICES review concluded that the greatest amount of evidence existed for the diagnosis and staging of lung cancer. None of the studies conclusively assessed the impact of PET scanning on overall patient well-being or quality of life, although intermediate outcomes such as

12. Institute for Clinical Evaluative Sciences. 2001 (May). Health Technology Assessment of Positron Emission Tomography (PET) – A Systematic Review. An ICES Investigative Report.

avoidance of thoracotomy in patients being considered for surgery were evaluated.[11] ICES concluded that the evidence for a role in the diagnosis of solitary pulmonary nodules was compelling when other diagnostic tests failed or were not applicable.

- Cardiology (heart): The ICES review found that PET could identify heart muscle that is dormant but still viable (so called "hibernating" myocardium) but there was no convincing evidence that PET was significantly better at doing this than other diagnostic tests. The review recommended against routine use of PET to assess cardiac viability but suggested that the evidence should be carefully monitored.
- Neurology: The ICES review found that PET had a limited role in the investigation of patients with intractable seizures who were being considered for surgery. There was no evidence to support the role of PET in diagnosing or managing dementia.

Ontario was faced with a dilemma. On the one hand, government was being asked to fund a new and expensive diagnostic technology that was claimed to improve care and save lives. On the other hand, a highly credible research organisation concluded – after an extensive review – that there was very little evidence to support the clinical value of the new technology. The lack of evidence and the uncertainty about the impact of PET on clinical decisions and patient outcomes could not justify using taxpayers' dollars to provide PET as a routine insured service.

The Ontario government decided to take an active role and establish an evaluation program to identify and support the areas where PET improves diagnosis and treatment decisions. Ontario's hospitals and their charitable research foundations supported Ontario's approach to PET scanning which included the following key elements:

- Access to PET through high quality clinical trials (5.1).
- Access to PET through registry studies (5.2).
- Access to PET through the PET Access Program (5.3).
- Quality assurance standards for PET (5.4).
- Ontario's PET infrastructure (5.5).
- Coordination of the PET program (5.6).
- Communications (5.7).

Each of these elements is described briefly below.

5.1 Access to PET through High Quality Clinical TRIALS

It is critically important to research the impact of PET technology on diagnosis and treatment decisions since these have a positive or negative impact on patient outcomes. The outcomes of the research – the research evidence – should then be used to guide clinical practice, which includes whether to use or not use PET scanning. Care must be taken to conduct good research and avoid biased results. Randomised clinical trials are recognised as the study design that best avoids bias when the effectiveness of interven-

11 "Metastatic" means that the cancer has spread beyond the original site of the disease.

tions is being examined.[14] Indeed, "tragedy can result from paying attention to poor quality evidence instead of good quality evidence."[15] The recommendations on the use of hormone replacement therapy (HRT) are a well known example of this. For many years, experts touted the benefits of HRT (estrogen) in reducing heart attacks in post menopausal women. When high quality randomized controlled trials were conducted, however, the results showed that HRT actually caused heart attacks.[16]

The ministry decided to support high quality clinical trials – designed by cancer experts – that would determine when PET improves diagnosis and treatment decisions. Cancer specialists (oncologists) in Cancer Care Ontario's Provincial Disease Site Groups were asked to review evidence on the role of PET in managing their disease site and to propose studies to improve the clinical management of patients.[17] These medical, radiation and surgical oncologists, nuclear medicine physicians and radiologists conducted a comprehensive evaluation and five PET studies for ministry support were selected (Table 1). The Ontario Clinical Oncology Group – affiliated with Cancer Care Ontario and located at McMaster University – worked with investigators to design, implement, and coordinate the studies and to collect and analyze the data from these trials.

- Early stage lung cancer (ELPET): This prospective randomized trial study examined patients who were potential candidates for complete surgical resection of their primary lung cancer. PET, CT and brain imaging were compared to the standard diagnostic workup recommended by Ontario thoracic surgeons (e.g., bone scan, CT of chest and abdomen, brain imaging). The Canadian Institutes for Health Research provided a grant to collect the data. This completed study of 337 patients found that the use of PET halved the rate of futile thoracic surgeries. As a result of the study, the ministry now supports PET scanning for early lung staging. This will increase the number of PET scans in Ontario by over 1,000 in the next 12 months. There has been a great deal of interest in the study and its results. On June 2, 2008, the study results were presented at the American Society of Clinical Oncology meetings and were chosen for special media profile. The study has also been presented at the Society for Nuclear Medicine annual meeting on June 15, 2008 where it won a Siemens Award for Excellence in Practice Based Research.

14 Dickersin, K., S.E. Straus and S.A. Bero. 2007. "Evidence based medicine: increasing, not dictating, choice" *British Medical Journal* 334 (Supplement 1: s10) http://www.bmj.com/cgi/content/full/334/suppl_1/A10 Accessed May 12, 2008.

15 Dickersin, K., S.E. Straus and S.A. Bero. 2007. "Evidence based medicine: increasing, not dictating, choice" *British Medical Journal* 334 (Supplement 1: s10) http://www.bmj.com/cgi/content/full/334/suppl_1/A10 Accessed May 12, 2008.

16 Hsia, J., Wallace, R., Anderson, G.L. et al. "Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin." *JAMA* 2008; 299 (9): 1036-1045.

17 Disease site groups in cancer include breast, gastrointestinal, genitourinary, gynaecology, head and neck, hepatobiliary and pancreatic, musculoskeletal, neurological, ocular, thoracic, haematology, and skin/plastic.

Table 1: PET Scanning Clinical Trials Supported by the Ontario Ministry of Health and Long-Term Care, August 31, 2008

Clinical Trial Study and Indication	Purpose and Study Design	Date First Site Started Patient Enrolment	Target Enrolment	Enrolment as of August 31, 2008
PET PREVENT Head and Neck Cancer	A prospective cohort study* to determine the ability of ^{18}FDG PET to detect metastatic cancer in neck lymph nodes in patients with head and neck cancer and in whom the cancer appears to have responded well to treatment. All enrolled patients will receive a PET scan before and after treatment.	May 5, 2004	400	359
PET START Stage 3 Lung Cancer	A prospective randomized controlled trial** to determine: i) whether PET will help detect if lung cancer has spread beyond the chest after the patient has undergone all the usual standard diagnostic tests; and ii) whether PET results will change the radiation treatment volume. Half the enrolled patients will receive a PET scan.	June 8, 2004	400	298
ELPET Potentially Resectable Lung Cancer	A randomized controlled trial** comparing standard imaging tests to PET and cranial imaging in the staging of clinically resectable non-small cell lung cancers to determine whether PET can detect occult metastatic disease and avoid futile thoracotomy. Half the enrolled patients will receive a PET scan.	June 1, 2004	322	347 (enrolment completed)
PET PREDICT Breast Cancer	A cohort study* to determine the ability of ^{18}FDG PET to detect the presence or absence of axillary lymph node metastases in newly diagnosed breast cancer patients with no clinical evidence of spread of disease.	January 7, 2005	320	336 (enrolment completed)
PET CAM Colorectal Cancer with Liver Metastasis	A prospective randomized controlled trial** to determine the impact of pre-operative ^{18}FDG PET on patients who have been assessed as having resectable colorectal cancer liver metastases by conventional imaging, by determining the proportion of patients who have a change in treatment management resulting from PET imaging. Half the enrolled patients (randomized to the PET arm) will receive a PET scan.	November 28, 2005	400	274
TOTAL				**1,604**

*All patients undergo PET scanning. **Half of the patients undergo PET scanning.

- Stage III (locally advanced) lung cancer (PET START): This second lung cancer study is a prospective randomized clinical trial to evaluate the role of PET and CT in staging patients with Stage III lung cancer who are potential candidates for combined chemotherapy and radiation administered with curative intent. The primary endpoint of this study is the proportion of patients who are upstaged and who would not be candidates for stage-appropriate radical chemo-radiotherapy. The study is also evaluating the role of PET-CT in radiotherapy treatment planning. As of August 31, 2008, there were 298 patients in the trial.

- Women with breast cancer (PET PREDICT): This breast trial was a non-randomized cohort study to determine the sensitivity of PET in detecting metastatic cancer in regional lymph nodes in women who had a biopsy. This completed study of 336 women found that PET is not sensitive enough to pick up tumours in the axillary nodes (nodes under the arm). The Steering Committee did not recommend the use of PET for this indication. These results were presented at the American Society of Clinical Oncology meetings in June 2008. The research team is analysing the data further. The false positive rate of PET for tumour in the axilla is very low, which means that if the PET is positive the surgeon can proceed to axillary node surgery.

- Head and neck cancer (PET PREVENT): This prospective cohort study will determine the sensitivity of PET in detecting metastatic cancer in the neck nodes of patients whose primary tumour had been managed with radiation therapy. If the PET examination is highly sensitive, lymph node dissection of the neck could be avoided. As of August 31, 2008, there were 359 patients in the trial.

- Colorectal cancer with metastases to the liver (PET CAM): This study is evaluating the role of PET and CT in defining which patients with metastatic colorectal cancer in the liver are appropriate for surgical resection of liver metastases. As of August 31, 2008, there were 274 patients in the trial.

Over 120 clinical experts across Ontario are participating in the five evaluation studies. Cancer Care Ontario, the Institute for Clinical Evaluative Sciences, oncologists, nuclear medicine specialists, the ethics review boards of each of the participating hospitals and the Ontario Health Technology Advisory Committee have endorsed Ontario's approach to these studies. Health Canada has also approved the studies, as required by federal regulations.

Each study needs a certain number of participating patients so the impact of PET scanning can be determined. The number of patients for each study has been determined by clinical trial experts based at McMaster University and Cancer Care Ontario's Ontario Clinical Oncology Group (OCOG). The number of patients in each trial has to be large enough to ensure that the results are scientifically valid. Various methods are being used to attract more patients to the ongoing trials such as broader patient entry criteria for inclusion in the studies, newsletters to oncologists and clinical research assistants, retreats with investigators, regular teleconferences of principal investigators, and including hospitals that do not have PET-CT machines on their sites. Despite these efforts, progress on enrolling patients has been slower than expected.

Access to PET through Registry Studies

In addition to the five clinical PET studies, Ontario decided to provide access to PET scanning where there is already enough evidence that the test improves diagnosis and treatment. Ontario must comply with Health Canada's regulations for the use of ^{18}FDG when providing this access to patients. As noted earlier, Health Canada regulates ^{18}FDG as a new product and requires a Clinical Trials Agreement for all non-approved indications. Currently, the only approved indication is for solitary pulmonary nodules which means that Ontario – and other provinces – have set up PET registries for cancer and cardiac to provide access to clinically-proven PET indications.

The Ontario Ministry of Health and Long-Term Care has established a cancer and a cardiac PET registry. Patients receiving PET scans for their cancer or cardiac conditions must be entered into one of these "registries" which includes information on the reason for and the results of the PET scan. Patients are also asked permission to link their registry data to other information located at the Institute for Clinical Evaluative Sciences. Almost all patients (97.9%) have given their permission to link the data on their care. Registry information will be analysed to determine patterns of care and patient outcomes after PET scanning.

Table 2 presents the indications and enrolments in the cancer and cardiac PET registries.

Table 2: PET Registries Supported by the Ministry of Health and Long-Term Care*

Name of Registry Study	Indications (Clinical Conditions)	Date First Site Started Patient Enrolment	Enrolment as of August 31, 2008
Cancer PET Registry	Solitary pulmonary nodule cancer Biomarker** positive, CT/MRI negative cancers: • recurrent thyroid cancer • recurrent colorectal cancer • recurrent germ cell cancers	July 2005 October 2005 October 2005 October 2005	1,917
Cardiac PET Registry	Left ventricular dysfunction being considered for revascularization or cardiac transplantation	2007/2008	141
TOTAL			**2,058**

*All patients undergo PET scanning **A biomarker – or biological marker – may indicate if disease is present

The results of the completed Ontario studies are used to inform which indications are included in the registry. The international research literature is also regularly reviewed for evidence that PET improves clinical decision making. The provincial disease site groups – working with Cancer Care Ontario's Program in Evidence-Based Care located at McMaster University – regularly examine the evidence and recommend if any new indications should be added to the PET registries. The Haematology Disease Site Group recently reviewed the evidence for using PET in malignant lymphomas and recommended that PET be used in two clinical circumstances. The Ontario Health Technology Advisory Committee has accepted these recommen-

dations and will add these indications to the PET registry (see Section 5). In addition, paediatric oncologists (cancer physicians who treat children) have reviewed the evidence on PET in childhood cancers and will recommend additional indications for the use of PET in the care of children with cancer.

5.3 Access to PET through the PET Access Program

In October 2006, the PET Access Program was established to review requests from physicians for a PET scan in those instances where the physician thinks the scan is justified but cannot be obtained through the clinical studies or registries. A review panel made up of an oncologist, radiologist and nuclear medicine physician assesses these requests. If approved by the panel, the PET scan is carried out in an Ontario institution which avoids an inconvenient and expensive out-of-country referral.

Any Ontario physician can refer a patient to the PET Access Program for review. Between October 2006 and March 31, 2008, 170 applications were received; 68 applications for a PET scan were approved by the panel. The most common clinical conditions for approval were lung cancer, colorectal cancer, lymphoma, melanoma and liver cancer. A number of these conditions are now covered through the cancer registry. Some of the referrals have been for patients where recurrent cancer is suspected but the diagnosis is unclear after the usual imaging tests have been done. This has led to the development of a sixth PET trial which will soon be recruiting patients. It has been common to have patients referred to the PET Access Program who have not had a standard work-up before PET is requested. Frequently the referrals have inadequate information to justify the use of PET and are sent back to the referring physician for additional information.

5.4 Quality Assurance Standards For PET

When the clinical trials were first being developed, there was limited experience with PET in Ontario. As well, there was a lack of consensus among nuclear medicine physicians and medical physicists about the most appropriate dose of the radiopharmaceutical ^{18}FDG to use, how best to perform a PET scan and how to interpret scans. Initially, there was wide variation in the interpretation of scans depending on who was reading the test results. To ensure consistent high quality standards, each PET image was read by a nuclear medicine physician from two different centres. This has helped reduce variations as physicians have gained more experience interpreting the PET scans. To ensure safety, accuracy, and consistency of PET scanning in the trials, quality assurance standards have been established and implemented for all PET equipment, physician training, imaging procedures, and image interpretation.

5.5 Ontario's PET Infrastructure

Ontario has one of the largest PET infrastructures in Canada. It includes 10 PET scanners located in academic health science centre sites in four geographic areas of the province (Table 3) and one private scanner located in Mississauga. Thunder Bay Health Sciences announced May 1, 2008, that it will acquire a PET/CT scanner and join the current PET evaluation studies. Seven of the scanners are used in the PET

evaluation studies. Not all of the clinical trials are conducted in each of the seven sites. (The two non-participating centres are The Hospital for Sick Children and the Centre for Addiction and Mental Health.)

Table 3: Location of PET Scanners in Ontario

Centre	Role	Local Health Integration Network
1. Hamilton: Hamilton Health Sciences Centre (McMaster University Medical Centre site)	Ontario-funded Clinical Trial Coordinates the PET Access Program	Hamilton Niagara Haldimand Brant
2. Hamilton: St. Joseph's Healthcare Centre	Ontario-funded Clinical Trial	Hamilton Niagara Haldimand Brant
3. London: St. Joseph's Healthcare Centre, London	Ontario-funded Clinical Trial	South West
4. Ottawa: The Ottawa Hospital (General site)	Ontario-funded Clinical Trial	Champlain
5. Ottawa: The University of Ottawa Heart Institute	Ontario-funded Clinical Trial Coordinates Cardiac PET Registry	Champlain
6. Toronto: Centre for Addiction and Mental Health	Hospital-based Research	Toronto Central
7. Toronto: Sunnybrook Health Sciences Centre	Ontario-funded Clinical Trial	Toronto Central
8. Toronto: The Hospital for Sick Children	Hospital-based Research	Toronto Central
10. Toronto: University Health Network (Princess Margaret Hospital site)	Ontario-funded Clinical Trial	Toronto Central
Toronto: University Health Network (Princess Margaret Hospital site)	Hospital-based Research	Toronto Central

To date, Ontario has provided over $8 million to fund the five clinical trials and the registry indications. This funding covers the PET scans for individuals who are in the clinical trials and in the PET registries, clinical trial staff salaries to collect the data, technician salaries, administrative and infrastructure costs, coordination and evaluation of the trials, screen reading fees and the radiopharmaceuticals (the largest expense). In addition, the ministry provided funding to the Program for Assessment of Technology in Health to conduct economic analyses of PET. Similarly, the Institute for Clinical Evaluative Sciences tracks the registry data. The hospitals buy the PET scanners on their own and share the operating costs with the ministry.

The cost of PET scanning includes the cyclotron to produce the isotope (one cyclotron can supply more than one scanner), the PET scanners, and the staff to maintain the cyclotron and scanner, manage the flow of patients through the scanner and interpret the imaging results. Published estimates of the cost of PET scanning in 2001[18] were $3-4 million for a cyclotron; $1.5 to $3 million for a scanner; $600 thousand a year

18 Institute for Clinical Evaluative Sciences. 2001 (May) *Health Technology Assessment of Positron Emission Tomography (PET) – A Systematic Review.* An ICES Investigative Report.

maintenance (for each scanner and cyclotron); $600 thousand a year for employee costs; and $250 thousand a year for other overhead costs.[19]

The cost of a PET scan varies depending on the distance between the scanner and the cyclotron, the efficiency of the scanner, and the number of scans from a batch of radiopharmaceutical produced. The average cost to perform a PET scan in Ontario is $1,000-$1,200 per scan which includes the cost of the radiopharmaceutical and a stipend (payment) for the nuclear medicine physician reading the scan.[20] The ministry continues to assess the funding level for PET scanning performed in Ontario's hospitals and has recently increased the funding-per-dose for the radiopharmaceutical used. In addition, effective October 1, 2007, patients residing in Northern Ontario who travel to Southern Ontario for a PET scan as a result of enrolment in the Ontario-funded PET trials or registry were eligible for the Northern Health Travel Grant.

Although it is difficult to estimate the future need for PET imaging, it is likely that the need will increase. The Royal College of Radiologists (United Kingdom) has suggested that there should be one PET/CT scanner for 1.5 million people.[21] This means that Ontario should have enough scanners at present to meet the needs of the province's 12 million people.

3.6 Coordination of the PET Evaluation Activities

A provincial PET Steering Committee makes recommendations on the appropriate use of PET in Ontario. The Committee is made up of representatives of the Institute for Clinical Evaluative Sciences, Cancer Care Ontario, and the Program for Assessment of Technology in Health, clinical oncologists, nuclear medicine physicians and experts in clinical research trials. The Steering Committee reports to the ministry's Ontario Health Technology Advisory Committee.

The Ontario Clinical Oncology Group – affiliated with Cancer Care Ontario and located at McMaster University – is well known for its expertise in cancer clinical trials research. The Group coordinates and manages the five clinical trials which include translating the clinical questions into research protocols, launching the trials at all centres, collecting and analyzing the data, and overseeing the implementation of quality assurance protocols and standards for the clinical trials. The Institute for Clinical Evaluative Sciences coordinates the PET cancer registry, Hamilton Health Sciences Corporation coordinates the PET Access Program, and the Ottawa Heart Institute coordinates the PET cardiac registry.

A PET Data Safety Monitoring Board – which is an arms-length board with members who are not involved in the clinical trials nor part of the Ontario Clinical Oncology Group – regularly reviews the data from the

19 Recent costing estimates provided by Dr. Karen Gulenchyn noted that maintenance costs are 10-12% of an imaging instrument's cost. Estimated annual costs for scanner maintenance are $230,000, for cyclotron maintenance $200,000, and employee costs $500,000. (June 6, 2008, email communication.)

20 Estimate provided by Dr. Leslie Lewis, April 3, 2008, email communication.

21 Royal College of Radiologists. 2005. PET-CT in the U.K.: a strategy for development and integration of a leading edge technology within routine clinical practice. London: Royal College of Radiologists.

trials and determines whether it is appropriate for the studies to continue. If the Board decides that there are clear differences between patient groups in terms of clinical outcomes and safety, the Board recommends that the trial be stopped.

5.7 Communications

Information about the clinical trials and registry studies has been regularly communicated to Ontario physicians through OHIP Bulletins. It appears, however, that some practitioners are not referring their patients because they do not know about Ontario's PET Program. The ministry and Cancer Care Ontario have increased PET communications by:

- Developing OHIP PET Bulletins which are sent to 29,000 Ontario physicians and posted on the OHIP website: http://www.health.gov.on.ca/english/providers/program/ohip/bulletins/4000/bulletin_4000_nn.html. The Bulletins include telephone contacts for additional information on the trials, registry and the PET Access Program.
- Funding a toll-free PET information line (1-877-4PET-411) and a permanent PET communication specialist at the Hamilton Health Sciences Centre to answer physicians' questions about accessing PET for their patients.
- Providing full information to patients and physicians about registering for a PET trial (all active clinical trials are registered on the Ontario Clinical Trials site).

6 What is the Definitive Evidence for PET Scanning?

Clinical experts in Ontario believe there is sufficient evidence that PET improves the diagnosis and treatment of patients for the following conditions:

- Solitary pulmonary nodules in cancer patients who cannot have a biopsy, who have failed prior biopsy attempts or in whom the potential risk of a biopsy-induced pneumothorax is high. PET is not recommended for all patients with solitary pulmonary nodules because histological diagnosis is still the gold standard in clinical care.
- Biomarker positive, CT/MRI negative recurrent thyroid cancer. These patients have a marker in the blood that is high (thyroglobulin) which suggests that their thyroid cancer has recurred; however, the results of their CT/MRI scans are negative. A PET scan may identify the location of the recurrent thyroid cancer and, if it is in one location (localized), the patient may have curative surgery.
- Biomarker positive, CT/MRI negative recurrent germ cell cancer. These patients have a marker in the blood that is high (elevated alpha fetoprotein or beta human chorionic gonadotrophin) which suggests that their germ cell cancer has recurred; however, the results of the CT/MRI scans are negative. A PET scan may identify the location and extent of the recurrent cancer, which will help determine the most appropriate and beneficial treatment.

- Biomarker positive, CT/MRI negative colorectal cancer. These patients have a marker in the blood that is high (carcinoembryonic antigen; CEA) which suggests that their colorectal cancer has recurred; however, the results of the CT/MRI scans are negative. A PET scan may help identify cancer metastases with a low rate of false positives and enable definitive and occasionally curative treatment.
- Myocardial viability studies. Patients who have poor function of their left ventricle (the main heart muscle) and whose treatment would either be revascularization or a heart transplant may benefit from a PET scan to identify "hibernating" cardiac muscle that can become functional with revascularization. If there is no viable cardiac muscle, the patient's only option is a heart transplant.

These five conditions are already included in Ontario's cancer and cardiac PET registries. It appears that PET scanning improves clinical decision making in two additional clinical circumstances which are in the process of being added to the cancer registry:

- Based on the results of one of the Ontario trials, PET with CT scanning of the chest and upper abdomen is recommended for patients who are being considered for surgical resection of their lung cancer. A PET scan can identify metastatic disease (cancer that has spread outside the chest) in more patients than is possible using conventional staging methods. PET and CT scanning help to ensure that only patients who have the potential to benefit from a surgical resection of their lung cancer actually have surgery (thoracotomy). The ministry has agreed to provide PET scans to Ontario patients with non-small cell lung cancer who are being considered for curative surgical resection.
- Lymphoma management: PET improves treatment decisions at two points in lymphoma management. These include: i) in early stage Hodgkin's lymphoma to assess the impact of chemotherapy and determine whether radiotherapy is also needed; and ii) to assess residual masses in patients who have completed standard therapy for potentially curable Hodgkin's lymphoma and non-Hodgkin's lymphoma and for whom further treatment is being considered.

7 What is the Experience of Other Jurisdictions?

The International Network of Agencies for Health Technology Assessment (INAHTA) conducted a survey of agencies providing PET in member countries in 2003/04.[22] Twenty-seven agencies from 19 countries that had some form of public funding for the clinical use of PET reported that this funding was often linked to collecting data to obtain evidence on the clinical use of PET and to better determine cost-effectiveness. For example, Australia funds promising FDG-PET indications on an interim basis to collect further data. At a 2004 workshop, the International Network of Agencies for Health Technology Assessment concluded that all countries need continuous quality improvement to manage the uncertainty about the evidence for PET. This requires systematic processes to collect data and regularly disseminate research findings to help providers use PET appropriately.

22 Facey K, L Bradbury, G Laking and E Payne. 2007. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess 11(44).

In the United States, PET scanners are widely available. There was a large increase in the number of scans when the U.S. Federal Drug Administration changed its regulations on the use of radioisotopes, and the American Medicare program and third party payers (insurance companies) increased funding for PET scanning. Medicare does not consider cost and cost-effectiveness in its decisions. The program routinely reimburses many indications for PET scanning. It has been estimated that the U.S. has over 1,600 PET scanning devices (5.3 PET scanners per million population), and that on average, 97% of Americans live within 75 miles of a clinical PET facility.[23] The estimated cost of a PET scan in the U.S. is between $3,500 and $6,000.[24]

The U.S. Centers for Medicare and Medicaid fund a number of approved cancer indications. For cancer indications which are not covered, the Centers have introduced a "Coverage with Evidence Development" policy which requires physicians to provide information on the usefulness of PET to clinically manage their patients with the conditions not currently covered. An internet-based National Oncologic PET Registry (NOPR) has been created to collect information on how PET affected patient management. To access a PET scan for their patient, physicians are required to complete a questionnaire describing the patient's medical condition (tumour type, stage, and patient's performance status), the indication for the PET scan and the referring physicians planned management if PET was not available. Following the PET scan, physicians are asked to assess the planned management in the light of the PET scan findings. Results were recently published on the questionnaire data from referring physicians on the intended management of patients before and after PET.[25] After one year, data were available on 22,975 studies, the majority using PET/CT (83.7%). The most common pre-PET plan would have been additional imaging. In these patients, the post-PET strategy changed to treatment in 48% and watchful full-up alone in 37%. The authors of the report noted that the post-PET strategy underwent a major change in type of management in 8.7% and in goal in 5.6%. One remarkable finding was that in approximately three quarters of patients where the pre-PET plan was to do a biopsy, the biopsy was not done post-PET. As pointed out by the authors of the report themselves, the failure to obtain a biopsy may reflect overconfidence in the PET results. The design of this registry study does not provide information on how much PET influenced clinical decision-making compared with standard management. Had PET not been available, it is possible that the other diagnostic studies the physician was contemplating (CT, MRI, nuclear medicine scan) might have led to the same clinical management decision.

Data in the NOPR can be linked to administrative data to evaluate patterns of care and outcomes but this has not yet been done. Information from NOPR may be used to stop payment for conditions where PET is not useful, or to pay for PET scans for those conditions where it is useful. At present it is being used by advocates to press for funding of a broader array of clinical indications.

The United Kingdom is moving towards funding 40,000 PET scans by 2008. The National Cancer Research Institute – a partnership of the Government Health Departments in the four countries of the U.K., three research councils, 13 charities and the Association of British Pharmaceutical Industry – recently released its

23 Rajendran, J.G. and B.E. Greer. 2006. Expanding role of positron emission tomography in cancer of the uterine cervix. INCON 4(5): 463-9.

24 Dr. Mark Levine. June 10, 2008, email communication.

25 Hillner, B.E., et al. 2008 (May 1). "Impact of Positron Emission Tomography/Computed Tomography and Positron Emission Tomography (PET) Alone on Expected Management of Patients with Cancer: Initial Results From the National Oncologic PET Registry." Journal of Clinical Oncology 26 (13): 2155-2161.

strategic plan for 2008-2013.[8] The Institute is undertaking a coordinating and leadership function which will network PET centres, develop collective solutions to overcome barriers, and ensure the development of common standards and practices for PET. The plan notes that this is "especially important for technologies that are expensive, multidisciplinary and where the evidence base for the clinical application is incomplete. In these circumstances, it is important to ensure that the limited capacity and resources available are used in the *most effective manner. The PET initiative may act as a prototype for how [the National The Cancer Research* Institute] can contribute to effective validation and implementation of complex technologies in other areas."

In Canada, all provinces – except for Quebec – have PET registries. In addition, British Columbia and Alberta conduct PET evaluation studies. Table 4 presents the results of a survey conducted in early May 2008, on PET scanning in Canada. The number of PET scanners in Ontario is more than any other province. However, the other large provinces (Quebec, British Columbia and Alberta) perform more scans. Ontario clinical experts believe that some of these PET scans are conducted for indications that do not have sufficient evidence of clinical benefit.

Table 4: Positron Emission Tomography (PET) Survey of Canadian Provinces/Territories, Survey Responses Provided as of May 9, 2008

Province/ Territory	MD Fee Code for PET?	Number of PET Scanners	Number of Cyclotrons	Number of Funded PET Scans 2007/08
Alberta	No	4	1	No direct funding. RHA global budget
British Columbia	No	1	1	3,100
Manitoba	No	1	1 being commissioned	2,000
New Brunswick	Yes	1	0	600
Newfoundland	No	0	0	None in province
North West Territories	No	0	0	Not provided
Nunavut	No	0	0	
Nova Scotia	No	1 planned late June 2008	0	Not Available
Ontario	No	10	3	No limit on approved indications
Prince Edward Island	No	0	0	12
Quebec	Yes	7 *	1	Capacity is 18,500 (existing facilities) but the actual # is not available
Saskatchewan	No	0	0	193
Yukon	No	N/A	0	18

* 5 additional sites approved but not yet in service ** 1 cyclotron anticipated.

• Regional Health Authority.

	Number of Funded PET Scans Actually Performed by April 7, 2008	Indications (Disease Conditions) Approved for Funded PET	Funded PET Scan Performed in Studies with CTA Approval
	April 1-December 31, 2007=2,900	Neurology & oncology	Yes
	2,855	www.bccancer.bc.ca/PPI/PET/indications.htm Non-Small Cell Lung Cancer, Lymphoma, Head and Neck Cancer, Colorectal and Testicula Carcinoma, Gynaecologic Cancer	Yes. Two clinical trials approvals: 1 adult and 1 paediatric
	1,000	Paediatric and adult oncology similar to Alberta and B.C. Neurology – Special Access	Yes
	500	All cancers except Gynaecologic	No
	Out-of-province: 33	Lung, Colorectal, Esophageal, Thyroid, Breast, Testicular, Melanoma, Neuroendocrine	N/A
			N/A
	Out-of-province		N/A
	Patients sent to Quebec on advice of oncologist	Cancers (unspecified)	
	1,255	See Tables 1 and 2 of this report	Yes
	Out-of-province	Based on recommendation of radiation & /or medical oncologists mostly for head & neck cancers	N/A
	18,500	98% oncology, and 2% neurology & cardiology (Oncology indications are Lung, Colorectal, Esophageal, Breast, Lymphoma and Thyroid)	
	Out-of-province 193	No restriction	N/A
	Out-of-province	Use B.C. or Alberta indications	Yes

8 Final Observations: The Critical Role of Evidence for Quality Patient Care

The Ontario Ministry of Long-Term Care's approach to providing PET scanning has been a contentious issue for nearly a decade. Some believe that PET should be widely available based on the claim that this technology improves care and saves lives. Others believe that PET should be used when it adds value and provides additional accurate information to improve the diagnosis and subsequent treatment of patients.

Clinical trials research is the best approach to obtain evidence for PET scanning. It has been suggested that PET is unfairly being held to a higher standard of evidence compared to other diagnostic tests such as CT and MRI. Concerns have also been raised in the media and elsewhere about the length of time it takes to conduct clinical trials.[27] For example, it has been suggested that the criteria being used for the studies may be too rigid and that if the ministry is going to base decisions about providing PET in Ontario on clinical trials, it should ensure that the studies are completed in a timely manner.[28]

Although the provincial approach to PET evaluation was launched in 2001, it has taken time to develop the necessary infrastructure for the clinical trials, develop the clinical protocols, get Research Ethics Board approvals, and develop quality assurance standards. It has also taken time to get enough patients in each of the trials due to a number of factors. Although over 75% of patients who are asked to enter a PET trial accept, some refuse because they simply want to get on with treatment and not have another diagnostic test. Many physicians may also want to start patient treatment quickly without knowing how PET might help in clinical decision-making. The studies depend on referrals from physicians who are encouraged to send their patients but are not told that they must send them. Low referral rates may also be due to scepticism and lack of support for the technology. Access to PET has become highly politicized and may have dampened the enthusiasm of physicians and surgeons to recruit patients. Finally, while the distribution of PET scanners in the province may mean that some people have to travel long distances, the scanners are mostly located in the most densely populated areas of the province.

Ontario is increasing its efforts to attract more patients to the trials such as broader patient entry criteria for inclusion in the studies, newsletters to oncologists and clinical research assistants, retreats with investigators, regular teleconferences of principal investigators, and the inclusion of hospitals that do not have PET-CT machines on their sites. To improve access to PET for clinically-proven conditions, Ontario – through the PET Steering Committee and Cancer Care Ontario – is urging Health Canada to simplify its regulations for accessing ^{18}FDG. As noted earlier, Health Canada regulates ^{18}FDG as a new product and requires a Clinical Trials Agreement for all non-approved indications. Currently, in Ontario, only Hamilton Health Sciences manufactures an approved ^{18}FDG product for lung cancer indications, including the diagnosis of solitary pulmonary nodules, staging of non-small cell lung cancer, and evaluation of recurrence in non-small cell lung cancer. This means that Ontario and other provinces have had to set up PET registries to provide access for other clinically-proven indications in cancer and cardiac disease.

27 Priest, L. 2008 (April 10). "Limiting cancer patients' access to medical test puts Ontario under microscope" Globe and Mail.

28 PET Scanning in Ontario: Deliberations of the University of Toronto Citizen's Council – Recommendations and Lessons Learned. Deliberations Conducted January 26-27, 2008.

Through Ontario's approach to the evaluation of PET, quality assurance standards have been established for all PET equipment, physician training, imaging procedures, and image interpretation. These standards have helped ensure safety, accuracy and consistency of PET scanning in the province. Ontario's PET clinical trials are – what the United Kingdom's Medical Research Council calls – complex clinical trials which are the most difficult to do. Although Ontario's clinical trials are taking time, they are resulting in high quality – and internationally recognised – evidence for the appropriate use of PET in diagnosis and treatment. This evidence is critically important for the safety and care of Ontarians. To illustrate, the gold standard for diagnosing cancer is a biopsy followed by a pathological examination. Although a recent study found that PET scanning will affect treatment decisions, it is unclear how these decisions will affect patient outcomes.[29] Of particular concern was the fact that 70% of patients who were scheduled to have a biopsy before a PET scan ended up not having a biopsy and having treatment based on their PET scan results alone. The PET scan was three times more likely to lead to treatment than non-treatment, with physicians changing the management of 36.5% of their patients after the PET scan. A potential over-confidence in PET scan results could undermine the standard practice in oncology without ever knowing how this affects patient outcomes.

Ontario remains committed to an evidence-based approach to the introduction of new technologies including PET. Given the competing demands for limited health care resources, the risks associated with diagnostic imaging procedures (all procedures have risks including the risk of false positive and false negative results), and the potential for the technology to affect patient outcomes significantly, it is reasonable to expect that PET's usefulness be established through high quality studies before it is used in routine clinical practice.[30] Making PET widely available would result in an additional cost to the system that – as evidence shows – would not be balanced by widespread additional benefits over and above current imaging techniques. Ontario's PET evaluation program is making a valuable contribution to the appropriate and effective use of this new technology in Ontario and internationally.

For Additional Information

Ministry of Health and Long-Term Care. 2008 (February 1). Bulletin 4464. Accessing Positron Emission Tomography (PET) Studies/Program Funded by the Ministry of Health and Long-Term Care, Ontario, Canada

- Attachment 1: PET Clinical Trials
- Attachment 2: Ontario Cancer PET Registry Study
- Attachment 3: Ontario Cardiac PET Registry Study
- Attachment 4: Ontario PET Access Program

www.health.gov.on.ca/english/providers/program/ohip/bulletins/4000/bulletin_4000_mn.html

29 Mittal, B.B. et al. (2008 (May 1). "Impact of Positron Emission Tomography/Computed Tomography and Positron Emission Tomography (PET) Alone on Expected Management of Patients with Cancer: Initial Results from the National Oncologic PET Registry." Journal of Clinical Oncology 26 (13): 2155-2161.

30 Institute for Clinical Evaluative Sciences. 2007 (May). Health Technology Assessment of Positron Emission Tomography (PET) – A Systematic Review. An ICES Investigative Report.

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